with limitation (ii) of step c) and limitation (ii) of step d) deleted. The deleted limitations are presented, hereby, as the subject matter of separate dependent claims 71 and 72, respectively, revised to better define the subject invention, i.e., as explained below.

> As recited in step c) of claim 52 (and present claim 70),
>
> the antisense oligonucleotide does not contain four or more consecutive elements capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target nucleic-acid sequence.

The "four or more consecutive elements of GGGG" recited in step c) were intended to "*alternatively*" define the excluded "four or more consecutive elements capable of forming three hydrogen bonds each with four consecutive cytosine bases," as recited in original claim 1 (*emphasis added*). In other words, the 4 or more consecutive guanine bases (GGGG) represent a preferred embodiment of the excluded subject matter (as described in the present specification, page 5, lines 7-9).

A similar situation is presented with respect to the subject matter excluded by limitation (ii) in step d) of claim 52. In step d)(ii) there are "three consecutive elements (GGG)," in "two or more series," intended to be excluded, instead of the "four or more consecutive elements" intended to be excluded in step c)(ii).

Accordingly, to more clearly define the excluded subject matter, present claim 71 recites "wherein the four or more consecutive elements not contained in the antisense oligonucleotide are each guanosine," and claim 72 recites "wherein the three consecutive elements in the two or more series not contained in the antisense oligonucleotide are each guanosine."

Claims 52-58 were rejected under 35 USC 103(a) for allegedly being obvious. Reconsideration is requested.

The statement of rejection evidences an apparent misunderstanding of the subject matter represented in the rejected claims. According to the statement of rejection, the recited "antisense nucleotide" does not contain four or more consecutive elements capable of forming three hydrogen bonds each with four consecutive *guanosine* bases within the target nucleic-acid sequence. Similarly, according to the statement of rejection, the recited "antisense nucleotide" does not contain two or more series of three consecutive elements capable of forming three hydrogen bonds each with three consecutive *guanosine* bases. The statement of rejection is mistaken in this respect.

As explained, above, the"four or more consecutive elements of GGGG" represent a preferred embodiment of the excluded "four or more consecutive elements capable of forming three hydrogen bonds each with four consecutive cytosine bases"; and, likewise, the "two or more series of three consecutive elements of GGG" " represent a preferred embodiment of the excluded "two or more series of three consecutive elements capable of forming three hydrogen bonds each with three consecutive cytosine bases." The "four or more consecutive elements of GGGG" do not define the number of A, C, T, or U nucleotides, i.e., GGGG is not an alternative for the "four consecutive cytosine bases (CCCC)." The "three consecutive elements of GGG" are not an alternative for the "three consecutive cytosine bases (CCC)."

The apparent misunderstanding may be the result of the manner by which original claim 1 was rewritten as claim 52 (in the Amendment filed April 15, 2002). The manner in which the

subject matter is represented in present claims 71 and 72 should clarify the apparent misunderstanding.

The presently claimed invention, thus, provides a rule for a rational design of oligonucleotides which are effective and non-toxic.

Milner et al. is not available as prior art against the present claims, since it was published **after** the priority date of the present application. Further, the reference discloses an empirical method for identifying oligodeoxynucleotide binding to a rabbit β-globin mRNA. As explained in the abstract, there was no obvious feature in the mRNA sequence that can explain the variation in duplex yield. Therefore, Milner teaches that the sequence is relevant, but Milner cannot predict what part of the sequence is relevant for effective and less toxic antisense sequences. Oligonucleotides prepared according to the invention are effective and non-toxic.

James summarizes the developments of antiviral antisense nucleic acids and ribozymes. He does not vie any information which sequence or primary structure is relevant for having effective and non-toxic oligonucleotides.

Smetsers et al. disclose that in some cases the effect of antisense oligonucleotides is to caused by an antisense mediated inhibition of translation of mRNA but by non-sequence specific effects. According to Smetsers this is caused by protein binding. Smetsers analyzed which sequences are used prior to the publication. The frequency of mono-, di-, tri- and tetra-nucleotides in antisense oligonucleotides were analyzed. According to page 64, right column, at the end of RESULTS, the motives GG, CCC, CC, GAC and CG are significantly higher in antisense

oligonucleotides then in randomly selected sequences. TT and TCC are much lower in antisense sequences. From table 1 one can see that GGG is frequently found in antisense oligonucleotides. According to the invention, there should not be two or more G triplets in the sequence. In the whole documents is no information that quartets of G and two or more triplets of G should be avoided to have an effective, non-toxic, specific antisense effect. Almost in contrast, there is an information on page 66, right column that a G quartet is effective in HIV inhibition. This is the contrary of what is the subject of the presently claimed invention.

Vaerman is not available as prior art against the present claims, since it was published **after** the priority of the present application. Further, the reference discloses that antisense oligodeoxyribonucleotides show increasing evidence of non-antisense cytotoxic effect (see Abstract, first sentence).

According to Vaerman, this effect is due to the toxicity of enzymatic hydrolysis products of the antisense oligodeoxyribonucleotides. D-GMP, TMP and d-AMP are cytotoxic, whereas d-CMP is not. He also investigated the influence of the two most terminal 3' positions of the oligonucleotide. From this document one cannot get any information whether quartets or triplets of guanosine should be included in the sequence or not.

Crooke (Ann. Rev. Pharmacol. Toxicol.) discloses therapeutic applications of oligonucleotides and some oligonucleotide sequences. In contrast to the statement of rejection allegation, the document does not disclose the rule for designing effective oligonucleotide disclosed in the present invention. Therefore, Crook lacks the rational design of oligonucleotides.

Baracchini discloses a number of oligonucleotides. Some fulfill the criteria of the presently claimed invention but some, for example, sequences 1 and 2, 11, 26 comprise four contiguous G. According to col. 8. Line 36, such oligonucleotides are even preferred. Baracchini does not disclose a rule for designing antisense oligonucleotides.

De la Monte et al. discloses methods of combining antisense oligonucleotides with hormones or lipids. This is relevant only for claim 57, i.e., only if the rejection against the generic claim is appropriate. The reference provides nothing to cure the fatal deficiencies against the generic claim.

According to the rejection (Office Action, page 6), "one of ordinary skill in the art would have been motivated to design and utilize antisense oligonucleotides comprising less than 2 C or G-triplets and comprising no G or C tetramers before the sequences of optimal antisense oligonucleotide sequences for a given target gene have routinely lacked such sequence configuration." This is not correct. Although prior art discloses oligonucleotides fulfilling the rule of the method of the presently claimed invention (free of G tetramers and two or more G triplets), this rule was not recognized in the prior art.

Prior to the presently claimed invention, oligonucleotides comprising G tetramers were even preferred, see Baracchini.

That this was not recognized is confirmed by Smetsers. Smetsers analyzed the frequency of mono-, di-, tri- and tetranucleotides. It would have been known to avoid G tetramers and G triplets, they should have a lower frequency compared to human coding sequences. In contrast, the

frequency of GGG is even higher than would be statistically expected (see Smetsers, table 1, line 3).

Request For Acknowledgment Of Foreign Priority Under 35 USC 119

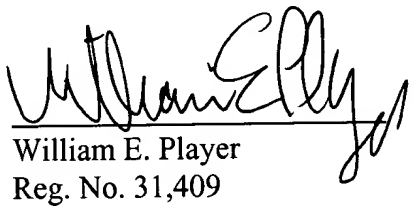
A claim to foreign priority under 35 USC 119 has been made (inventorship declaration, filed October 7, 1999) and the certified copy of the priority document received by the PTO (Notification of Acceptance, mailed August 24, 1999, by the PTO, and Form PCT/IB304, mailed 22 April 1998 by the International Bureau, of record).

Accordingly, request is made that the Examiner mark the next Office Action to acknowledge, both, the claim to §119 priority and receipt of the certified copy.

Favorable action is requested.

Respectfully submitted,

JACOBSON·HOLMAN PLLC

By: 

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